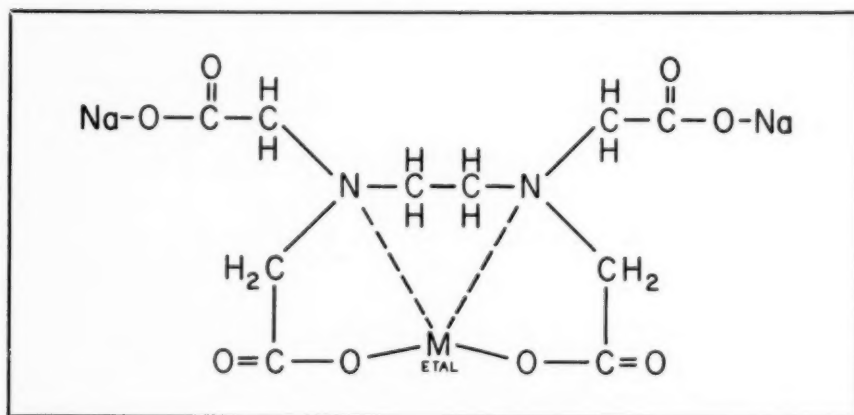


American Journal of Pharmacy

AND THE SCIENCES SUPPORTING PUBLIC HEALTH



STRUCTURE OF A CHELATE

(See article p. 198)

Bacteriology - - Biology
Chemistry - - Pharmacy



Founded 1821

Undergraduate courses of study in these four health sciences help prepare for interesting and successful careers. Selected Graduate studies available also. Co-educational. Classes commence each September.

Current catalog available on request.

Philadelphia College of Pharmacy and Science
43d Street, Woodland and Kingsessing Avenues
Philadelphia 4, Pa.

American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription \$4.00
Single Numbers, 40 Cents

Foreign Postage, 25 Cents Extra
Back Numbers, 50 Cents

Entered as Second-Class Matter March 27, 1937, at the Post Office at Philadelphia, Pa.
Under Act of March 3, 1879

permits better control for
the majority of diabetics

NPH INSULIN

NPH Iletin (Insulin, Lilly)

**moderately long-acting
carefully standardized**

For Intermediate Effect: (affords best control for most patients) NPH Iletin (Insulin, Lilly), U-40 and U-80

For Rapid Effect: Iletin (Insulin, Lilly), U-40, U-80, and U-100 • Iletin (Insulin, Lilly) made from Zinc-Insulin Crystals, U-40 and U-80

For Prolonged Effect: Protamine, Zinc & Iletin (Insulin, Lilly)—Protamine Zinc Insulin—U-40 and U-80

IN 10-CC. VIALS, 10 VIALS IN A CARTON

Lilly

**ELI LILLY AND COMPANY
INDIANAPOLIS 6, INDIANA, U. S. A.**

prescribed to brighten the patient's outlook



AMPHEDASE* KAPSEALS®

NEW antidepressant and nutritional adjunct

When depression, fatigue, and faulty food intake threaten to prolong convalescence, AMPHEDASE is prescribed as a valuable adjunct. The patient's mood is elevated and attendant fatigue lessened.

In ordering stock, remember the many indications for which physicians are prescribing AMPHEDASE: asthenia, convalescence, depression, chronic alcoholism, geriatric therapy, and faulty nutrition.



each AMPHEDASE Kapseal contains:

d-amphetamine sulfate	2.5 mg.
Nicotinamide	25.0 mg.
Thiamine hydrochloride	5.0 mg.
Ascorbic acid	50.0 mg.
Taka-Diastase	300.0 mg.

Supplied in bottles of 100 and 500 Kapseals.

More detailed information on AMPHEDASE is available from the Parke-Davis sales representative who calls on you.

*TRADE-MARK



Parke, Davis & Company
DETROIT, MICHIGAN

AMERICAN JOURNAL OF PHARMACY AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

LINWOOD F. TICE, Ph. G., M. Sc., D. Sc., Editor
Kenneth Avis, M. Sc., Editorial Assistant
Charles E. Welch, Jr., B. S., M. A., Editorial Assistant
John E. Kramer, B. Sc., Business Manager

COMMITTEE ON PUBLICATION

E. Fullerton Cook, P. D., Ph. M., D. Sc., Chairman
Mitchell Bernstein, P. D., M. D., F. A. C. P.
Marin S. Dunn, A. M., Ph. D.
Louis Gershenfeld, P. D., Ph. M., D. Sc.
Joseph W. E. Harrisson, P. D., Sc. D.
Ivor Griffith, P. D., Ph. M., D. Sc., F. R. S. A., ex officio

Vol. 126

JUNE 1954

No. 6

CONTENTS

Editorial

The Support of Fair Trade 192

Articles

An Evaluation of Prantal Cream in Localized Hyperhidrosis. By Arthur G. Zupko 194

Organic Metal Co-ordinate Compounds. By Gordon A. Bergey 198

Selected Abstracts 217

EDITORIAL

THE SUPPORT OF FAIR TRADE

THOUSANDS of pages have been devoted in various journals to the subject of Fair Trade; it would seem that there is little left to be said on this important subject. While not engaged in retail pharmacy, we can well remember the chaos which existed in the days before Fair Trade, and the economic strangulation which was in operation on all small businessmen. We can also remember how "loss leader" selling by retailers hurt the sales of nationally known brands and led manufacturers to endorse the establishment of minimum resale prices and Fair Trade contracts for their own protection.

At a recent state pharmaceutical meeting we were somewhat aghast to learn that all too frequently certain retail pharmacists who loudly proclaim the merits of Fair Trade, themselves violate its terms surreptitiously. This they do not on altruistic grounds to help some very poor customer but as a means of gaining an unfair trade advantage over their nearby competitors.

We can understand the opposition to Fair Trade by certain large chains and supermarkets for it is this legislation indeed which makes it possible for the small businessman to compete in the retail market. It is difficult, however, for us to envision a small retailer who is so selfish and so lacking in vision that he purposefully and deliberately undermines the very legislation which keeps him in business. Truly there is much about certain members of the species *Homo sapiens* which is akin to the behavior of *Sus scrofa*.

Fair Trade is of much greater importance to us as Americans than it is to us as pharmacists. Should that dark day come when our enabling legislation is rescinded much more will be lost than our economic welfare. The growth of giant chains and supermarkets, already alarming, will increase very rapidly and soon dwarf into insignificance all other retail outlets. But some will say, "Why not"? "Are they not more efficient?" They may well be but this should not be the final consideration in judging all things. If and when prac-

tically all retail purchases are made in giant supermarkets, owned and operated by a few large corporations, great social and political changes are apt to occur. By their very greatness they will sow the seeds of their own destruction. Now, instead of thousands of voters owning businesses in the retail field only a comparative few will. This will lead to great public pressure for the government to own and operate these enterprises. We can then expect political demagogues to attack these "rich, greedy corporations" and it will be sweet music to the voters' ears.

The concentration of economic power in ever-growing large corporations like the concentration of power in great labor unions hastens the day when we shall see an end of our system of free enterprise. By the same token all legislative action directed toward the preservation of small business and against the exercise of unrestrained power by unions, strengthens our economic system and the prerogatives of the individual.

Large corporations tend to grow larger and strong unions stronger. In neither is there much likelihood that these words or any others from whatever source will cause them to cease their efforts towards greater growth. The restraint, if it is to come, must come from those who can foresee the results predicted and whose immediate survival is at stake. Small businessmen should be among these without a single disaffection. Those who weaken Fair Trade have a moral responsibility to mend their ways and to support it with more than lip service.

While there are many and increasing numbers of Americans who see nothing wrong or threatening in the concentration of power it is by its very nature a threat to each and every individual. Americans who believe in personal freedom and the dignity of the individual must act to prevent the concentration of power in business, in unions and indeed even in government itself. Each of these in turn must guard against the unbridled use of power by either of the other two. Fair Trade legislation is a just and proper restraint on corporations which without it would be a threat to our present system of retail distribution. This is an essential and vital part of our system of free enterprise. Pharmacists who do not support it by action as well as words are guilty of destroying the future of retail pharmacy and rendering a disservice to their country.

L. F. TICE

AN EVALUATION OF PRANTAL CREAM IN LOCALIZED HYPERHIDROSIS¹

By Arthur G. Zupko, Ph. D.*

SEVERAL reports have appeared (1-5) which indicate the effectiveness of orally administered anticholinergic agents in controlling generalized hyperhidrosis. Recently one of these anticholinergic agents, Prantal (N,N-dimethyl-4-piperidylidene-1, 1-diphenylmethane methyl sulfate), was introduced to the medical profession in topical form, the first of the newer anticholinergics to be offered as a cream for use against localized hyperhidrosis.

Certain areas of the body possessing large numbers of sweat glands such as the palms, soles, forehead, axillae, etc., are vulnerable sites for localized hyperhidrosis, especially under the influence of excessively elevated temperatures, stress, or autonomic imbalance. Since existing dermatological conditions at these sites are aggravated by the irritating effect of continued sweating, it is apparent that any topically applied agent capable of inhibiting sweating with minimal side effects would be of immense value.

In view of the fact that oral administration of anticholinergics is accompanied by such systemic side effects as mydriasis, xerostomia, gastric irritation, and headache (1-5), it was deemed advisable to evaluate Prantal cream in order to ascertain the side effects resulting from topical application as well as the efficacy of this form of Prantal administration in controlling localized hyperhidrosis.

Experimental

Prantal cream containing 20 mg. of Prantal per gram of a water-washable base was applied topically to a total of 204 subjects, divided into three groups. Group I included 55 subjects with localized hyperhidrosis affecting various areas of the body. This group applied Prantal cream three times a day to the affected areas at four-hour intervals. Group II consisted of 138 normal subjects, 66 of whom

1. The Prantal cream used in this study was supplied by Dr. George Babcock of the Schering Corporation, Bloomfield, New Jersey.

* Associate Professor, Department of Physiology and Pharmacology, St. Louis College of Pharmacy and Allied Sciences, St. Louis 10, Missouri.

were practicing pharmacists and 72 students actively engaged in writing, studying, or participating in laboratory work requiring dry hands (handling capsules, etc.). This group used the Prantal cream as required, but at least once daily. Group III was composed of 11 professional major league baseball players actively engaged in a pursuit calling for strenuous muscular effort. These athletes applied the medication approximately 15 minutes before game time.

Each of the groups used the medication daily for periods ranging from two to six weeks. In addition several subjects from each group were given a placebo cream containing the water-washable base without Prantal. All experiments were performed during the late spring and summer of 1952 and 1953.

Subjects were examined and queried at frequent intervals to determine the effectiveness of the cream as well as any side effects or sensitivity reactions resulting from topical application of the cream.

Results

The effectiveness, side effects, and sensitivity reactions resulting from the use of Prantal cream are summarized in Table I.

TABLE I
REPORTED EFFECTIVENESS, SIDE EFFECTS, AND SENSITIVITY OF
PRANTAL CREAM

Group No.	Number of Subjects	Reported Effectiveness		Number Reporting Side	
		Yes	No	Effects	Sensitivity
I	55	34	11	0	1
II	138	73	65	1	1
III	11	1	10	1	0

Effectiveness.—One hundred and eight subjects or 52.9% reported satisfactory inhibition of sweating, including 34 hidrose subjects or 62.8% in Group I, 73 normal subjects or 52.9% in Group II, and only one athlete or 9.1% in Group III. Topical application of a placebo cream in 18 subjects did not elicit an anhydrotic response.

Side Effects.—Systemic side effects such as dysuria, xerostomia, tachycardia, and headache which accompany oral anticholinergic therapy were not observed with Prantal cream. Two subjects or

less than one per cent of the 204 subjects exhibited a mild degree of mydriasis. One of these subjects was in Group III and the resultant mydriasis interfered with his athletic performance to a sufficient degree to force him to discontinue the medication.

Sensitivity.—Evidence of sensitivity to Prantal cream was discernible in less than one per cent of the subjects. A mild degree of erythema was noted at the sites of application in two subjects. No other signs of irritation were in evidence. In both cases the erythema disappeared within 48 hours after discontinuance of the medication.

A third subject who exhibited signs of irritation with the Prantal cream was also sensitive to the placebo cream.

Discussion

Although apparently inducing a localized anticholinergic effect, the mechanism of action of Prantal cream is unknown. Whether the medication has some effect on cell membrane permeability or the anticholinergic action depresses the liberation of fluids in some other manner is conjectural.

The cream does not appear to be efficacious in controlling sweating in individuals performing strenuous exercise, as evidenced by the results obtained with the subjects in Group III. As with any medication, if the stimulus is great enough the inhibitory effect of the drug is overcome.

In spite of the fact that only less than one per cent of the subjects exhibited mydriasis, this effect is an indication that Prantal cream should not be used on skin surfaces which are either abraded or denuded. Use of the cream under such circumstances would enhance absorption and increase the likelihood of additional side effects.

The anhydrotic effect of Prantal cream may be used to advantage in a variety of dermatological conditions. It should be emphasized, however, that the cream affords only temporary relief and must be applied at suitable intervals for adequate control of sweating.

Summary

1. Two hundred and four subjects applied Prantal cream daily to various parts of the body for periods ranging from two to six weeks.
2. The medication proved to be effective in controlling localized hyperhidrosis in 108 subjects or 52.9%.

3. Prantal cream was ineffective in inhibiting sweating in subjects performing strenuous exercise.

4. Side effects and sensitivity reactions occurred in less than one per cent of the subjects.

5. Prantal cream affords temporary relief and must be applied at suitable intervals for adequate control of sweating.

REFERENCES

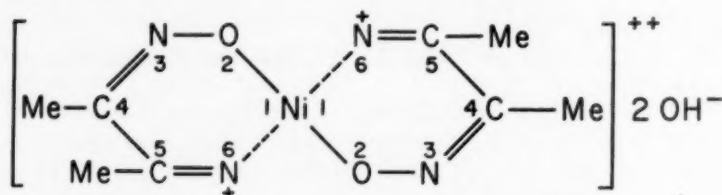
- (1) Nelson, L. M.: *J. Invest. Dermat.* 17, 207 (1951).
- (2) Nelson, L. M.: *J. Invest. Dermat.* 18, 373 (1952).
- (3) Zupko, A. G.: *J. Am. Pharm. Assoc. (Sci. Ed.)* 41, 212 (1952).
- (4) Zupko, A. G. and Prokop, L. D.: *J. Am. Pharm. Assoc. (Sci. Ed.)* 41, 651 (1952).
- (5) Zupko, A. G. and Prokop, L. D.: *J. Am. Pharm. Assoc. (Sci. Ed.)* 43, 35 (1954).

ORGANIC METAL CO-ORDINATE COMPOUNDS

By Gordon A. Bergy *

THE subject of organometallic ring compounds, or chelates (key-lates) was early dealt with by Diehl (*Chem Reviews*, 21, 39 (1937) who using the terminology of Morgan, classified the compounds as bidentate, tridentate, etc., according to the number of links of "teeth", and further differentiates as to whether the bonds are primary (from acidic groups), secondary (co-ordinate), or a mixture of both. Calcium fell among the elements of his system which have a coordination number of six and a primary valence of two.

One of the earliest chelating agents with which most students in chemistry have formed an acquaintance is dimethyl glyoxime the reagent used for the detection of nickel ion by its green color.



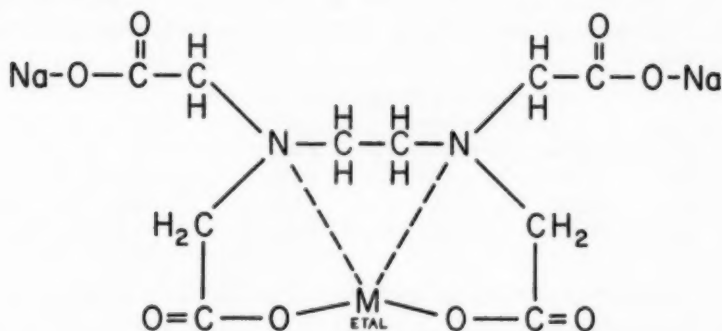
Two ordinary and two coordinate bonds of nickel exist.

After the nickel has attached itself to one molecule of the dimethylglyoxime by replacing the OH hydrogen, the N at the other end of the chain is in the 1-6 position of the Ni atom and therefore near it in space. It might be thought that the Ni would replace the other H and give a compound with one atom of Ni for one molecule of the dioxime. Such does not happen as it would necessitate the formation of the 7 membered ring.

Thus the Ni forms a complex ion in which it acts as the common atom in the spire system. Six membered rings of this type in which the closure is through subsidiary valences of elements like oxygen, nitrogen and the metals are common in organic chemistry. They are chelate rings.

* School of Pharmacy, West Virginia University.

Ethylene diamine tetra-acetic acid with metals likewise form chelate rings.



Patents have been issued on the preparation and use of amino-polyacetic acids and certain respective salts. Pfeiffer prepared their calcium derivatives; and the investigations of Schwarzenbach and his co-workers did much to measure and clarify the action of these acids in reducing the availability of calcium ions.

The amino-polyacid amines will inactivate practically any metallic ion which they contact, usually the higher the valence and the higher the pH the greater the tendency for chelating or complexing. As the pH is reduced the stability of the chelate decreases. Below a pH of 7.5 calcium and magnesium are not complexed efficiently. At a pH below 5 the strength of the calcium complex is not sufficiently great as to prevent the precipitation of the calcium ion as oxalate.

Copper on the one hand is 50% chelated at a pH of 2 and practically 100% chelated at a pH of 3.5. All other common metal ions are efficiently complexed between the values of 3.5 and 7.5.

Calcium phosphate, calcium oxalate, barium sulfate and magnesium carbonate are a few of the many metallic precipitates which may be dissolved by the amino-polyacidamine sodium salts. This affords control of foreign metallic ions in industrial processes. The non-removal of these metallic salts hastens the development of rancidity, odor, coloration, decomposition and many other undesirable reactions in both processes and finished products. They are stable and inert toward attack of all chemical compounds with the exception of the strong oxidizing agents which convert them to ureides.

Metallic ion response to chelation will be preferential. A metallic ion which is capable of forming a stronger chelate will displace another metal less firmly bound. The order of chelation of the common metals at their optimum pH values is introduced for study because of its brevity.

TABLE I

pH	4.00	Cr	Cu	Ni	Pb	Co			
pH	6.50	Ni	Cu	Co	Zn & Cd	Ca			
pH	8.65	Ni	Co	Cu	Zn & Cd	Ca	Mg	Sr	Ba
pH	11.00	Co	Ni	Cu	Zn & Cd	Ca	Mg	Sr	Ba

Because of preferential chelation the amino polyacid amines can be advantageously used in the purification of many solutions by inactivating some metallic ions in the presence of others. To illustrate, if an acid nickel sulfate solution is contaminated with a small amount of copper, the copper may be chelated preferentially leaving the nickel unchanged. The solution of nickel salts may be crystallized or precipitated free from copper, since the copper chelate compound will not form mixed crystals or react with common precipitating agents. The preparation of calcium-free magnesium by permitting the precipitation or crystallization of pure magnesium compounds is another example. This same general procedure is applicable to many separations—including the rare earths and the development of new analytical procedures.

The amphoteric metals are complexed by the polyacid amines. They are aluminum, chromium and zinc. The mechanism of this reaction is not as straightforward as it is with the non-amphoteric group. In acid solution a slightly larger quantity will be necessary due to the reduced efficiency of the polyacid amines in acid solution. Five hundred grams of the agent will be required to inactivate one mole of amphoteric metal. In the way of illustration, soluble aluminum compounds will precipitate aluminum hydroxide as the pH is increased. Precipitation is complete in weakly acid solution. If additional sodium hydroxide is added, the precipitate will dissolve forming sodium aluminate. If more complexing agent is added to the aluminum solution, no precipitate will occur when the pH is raised even though an insufficient amount of alkali be present to form the aluminate. If a sufficient amount of alkali be present to initiate the

formation of aluminate, some of the chelated aluminum ions will be released and the aluminate will form. This conversion will be extended until all the aluminum is converted to the aluminate. If a sufficient amount of complexing agent be present no precipitate will be formed at any stage. The process is also reversible.

Two complexing or chelating agents are now commercially available. A handful of other agents of lesser efficiency aside from the citrates are of academic interest. These will be discussed briefly in subsequent paragraphs.

Versene is the trade-marked name of the tetra sodium salt of ethylene diamine tetra-acetic acid. It is a product of the Bersworth Chemical Co., of Framingham, Mass. *Sequesterene* available as the pure acid, di, tri and tetra sodium salts is the trade name of the Alrose Chemical Co., Providence, Rhode Island. The same product is also manufactured by the General Dyestuff Corporation, 435 Hudson St., New York, as the *Nullapons*.

The polyacid diamine readily dissolves in alkali to form the di, tri, and tetrasodium salts which have pH values for 1% solutions of 4.8; 8.8 and 11 respectively. The disodium salt is soluble to the extent of only 3%, but the tri and tetrasodium salts are very soluble.

SODIUM POLYPHOSPHATE OR GRAHAM'S SALT

In 1849, the German Chemist Rose made the following statement: "No substance offers the chemist greater difficulties than does phosphoric acid; the more the behavior of the acid is studied, the more the difficulties increase. Every new investigation presents the chemist with new anomalies." Each year reveals new uses for the phosphates particularly in the fields of fertilizers, insecticides, detergents and water conditioning agents. Chemists in general regardless of their fields of specialization are becoming more concerned about the differentiation between the various forms of the phosphates, the properties and structures of these forms, analytical procedures for determining their compositions and concentrations, and their interferences in analytical procedures for other constituents.

In 1833, Thomas Graham a British Chemist and founder of the field of colloid chemistry discovered a new form of phosphate which become known as Graham's Salt. It has a glassy or amorphous form and has the empirical formula NaPO_3 with a molecular ratio of 1

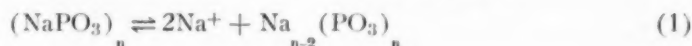
$\text{Na}_2\text{O}:\text{1P}_2\text{O}_5$. It can be made as Graham made it, from the monosodium dihydrogen phosphate, NaH_2PO_4 , by heating to drive off a molecule of water, then fusing, and finally chilling suddenly by pouring the melt on a cold metal surface. The clear colorless product is soluble in water in all proportions to form an unbuffered nearly neutral solution. It is distinguished from the pyrophosphate and the orthophosphate forms by its ability to precipitate with egg albumin. In 1849 Fleitman concluded on what must be termed insufficient evidence, that this material was a "hexametaphosphate". For eighty years this salt remained virtually a laboratory product its principal application being the well known metaphosphate bead test developed by Emerson in 1866. Hall & Jackson first produced and used the chemical commercially in 1929 for boiler water conditioning, and Hall announced his discovery in 1932 of its property of softening water without precipitate formation and without the removal by precipitation of the constituents causing hardness. Graham's Salt has been tagged the "Cinderella of the Phosphates". Much has been learned about its properties but comparatively little has been known about its structure. It is however known not to be a "hexametaphosphate" as claimed by Fleitman. Probably its structure is that of chains of varying length intertwined resembling very much the organic polymers. Graham's Salt is referred to as a glassy or vitreous phosphate, a molecularly dehydrated phosphate and a polyphosphate, these terms serving to distinguish it from the parent orthophosphate.

Three properties of glassy sodium metaphosphate are sequestration, dispersion and dilatancy, the third being a laboratory curiosity with no commercial application at present. The commercial glassy sodium phosphate "Calgon" is a modified Graham's Salt characterized by a molar ratio of about 1.1 Na_2O to 1 P_2O_5 . The slight increase in Na_2O makes its solution more nearly neutral and improves its rate of solution.

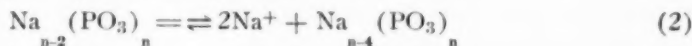
The term sequestration as applied to the softening of water is of recent origin. The word itself means the act of retiring, secluding or withdrawing into obscurity or the act of taking possession of, by confiscating or appropriating. In the chemical sense, sequestration is the reduction of the concentration of a multivalent positive ion in solution, by combination with a negative ion, to the extent that the remaining concentration of the multivalent positive ion is insufficient to be precipitated by a given negative ion with which it has a low

solubility product constant. The sequestration value is a stoichiometric ratio of weight relationship expressed as the quantity of a sequestering agent required to capture a unit quantity of a multivalent positive ion and form with it a complex negative ion which is stable against precipitation by a given precipitant by the multivalent positive ion. In sequestration the multivalent positive ion has practically disappeared from the solution without being evolved as a gas, removed as a precipitate or deposited as an element.

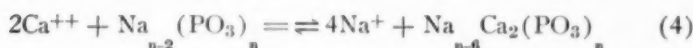
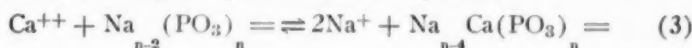
The phenomenon of sequestration can best be explained by the sequestration of Calcium ion by Graham's Salt. Hall, the first to discover this property, speculated that this glassy sodium metaphosphate might produce a primary ionization as follows:



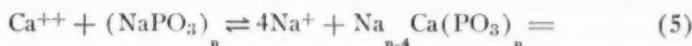
and possibly a secondary ionization as follows:



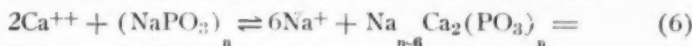
The subscript n represents the number of NaPO_3 units comprising the polymeric molecule in solution. With calcium ions, the following metatheses or changes of partners would be possible:



By combining equations (1) and (3) the following equation results:



By combining equations (1) and (4), the following equation results:

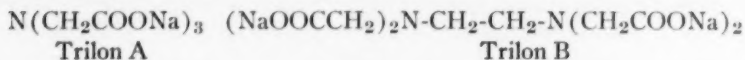


Equation (5) shows one calcium ion, and equation (6) two calcium ions, sequestered by one polymeric sodium metaphosphate molecule. The number of calcium ions which can be sequestered by one polymeric sodium metaphosphate molecule is dependent upon the value of (n) and upon the ionization constants of the complex negative ions formed.

In any event, by an ion exchange, similar to the base exchange reaction of zeolites—but occurring entirely in solution, each positive calcium ion replaces two sodium ions in a complex negative ion. The calcium ions remaining as such would be the equilibrium concentration represented by the reserve of reaction of (3) and (4).

To demonstrate that this residual calcium ion concentration is very low may be shown by adding soap which normally forms a very insoluble salt with calcium ions, but which will not concentrate with calcium when sufficient Graham's Salt is present. Conversely the glassy sodium metaphosphate will dissolve precipitated calcium soap. Thus the concentration of calcium is no longer present in more than a minute trace, of the order of a few parts per million.

Certain other materials than the glassy polyphosphates also are capable of sequestration, in general to a lesser degree. Of the phosphates, crystalline sodium pyrophosphate, $\text{Na}_4\text{P}_2\text{O}_7$ or $\text{Na}_2\text{H}_2\text{P}_2\text{O}_7$, crystalline sodium tripolyphosphate $\text{Na}_5\text{P}_3\text{O}_{10}$ and sodium phytate $\text{C}_6\text{H}_6(\text{Na}_2\text{PO}_4)_6$ (also called inositol hexaphosphate) from corn steep liquor, are the more common examples. Likewise certain organic compounds which contain no phosphorus have been found to exhibit sequestration, among which may be mentioned the *Trilons* which have the following formulas:



The phenomenon of sequestration is not just a laboratory curiosity, it has found extensive usage in softening water which is to be used with soap. All natural water, with the possible exception of rain water, contains some calcium and magnesium ions, and these form quite insoluble precipitates or scums with soap. Before a soap can form the lather, which is an attribute of the alkali metal soaps, it must first be added in sufficient amount to precipitate the calcium and magnesium ions, these being the so-called hardness constituents. By the use of a sequestering agent, this precipitation can be prevented and a lather formed with considerably less soap. Hence sequestration can be employed in laundering, in dishwashing, and in every cleaning operation where soap and water are used. In fact sequestration was employed in removing the radio-active residues from pigs exposed at the Bikini Atoll atomic bomb test.

Dispersion signifies the state of suspension of finely divided particles in some other substance. The following dispersions, with typical examples, are possible:

<i>System</i>	<i>Example</i>
Solid in solid	Antimony in lead
Solid in liquid	Colloidal graphite in water or oil
Solid in gas	Smoke in air
Liquid in solid	Iron amalgam
Liquid in liquid	Oil in water emulsion
Liquid in gas	Cloud-water in air
Gas in solid	Hydrogen in steel
Gas in liquid	Whipped cream

In colloidal dispersions, the particles do not settle appreciably under the influence of gravity, but the particles of a coarse colloidal dispersion or of a coarse suspension do settle slowly. Under ordinary conditions the particles are prevented from coalescing by possessing an electric charge, the origin of which is still a matter of controversy. In a solid-liquid dispersion, the charged particles will travel to the anode or the cathode (depending upon the sign of the charge) when subjected to a unidirectional current. They do not conform to Faraday's Law in that 96,500 coulombs of electricity liberate more than one gram-equivalent and often up to six or eight times this amount of the material. When the charge is removed, as by the addition of electrolyte, the particles coagulate or flocculate and the sol (i.e. the colloidal solution) forms a flocculated system (where the solid particles are clustered together) settling rapidly, leaving a clear liquid layer with a sharp dividing line between the liquid and the solid phase. A deflocculated system (solid particles geometrically independent and unassociated with adjacent particles) settles slowly, leaves a cloudy or liquid layer usually with no sharp dividing line between the liquid and solid phase.

Solid-liquid and liquid-liquid dispersions are of great industrial importance and particularly those employing water as the dispersion medium. A few of the familiar dispersions may be cited: paints, pigments, printing inks, paper and textile coatings, liquid polishes, dentifrices, emulsion cleaners, milk of magnesia, laundry starch, glues, mayonnaise, ceramic slips or flotation media, oil well drilling muds,

and insecticidal sprays. In aqueous dispersions, Graham's Salt serves a multiple purpose: that of sequestering multivalent ions which would otherwise flocculate the dispersion or break an emulsion, that of reducing the viscosity of dispersions containing a high total solids content, and that of retarding settling of dispersions.

In pharmaceutical procedure the dispersion of finely divided metal oxide and salt pigments, such as kaolin, clay, titanium dioxide, calcium carbonate, lithopone, zinc oxide, talc and barium sulfate can be improved and the settling rate materially retarded by the use of very small quantities of Graham's Salt, the amount required being dependent upon the type of pigment, the pH of the slurry, and the solids content of the slurry. This action is probably due to the strong adsorption of the phosphate on the surface of the particles which increases their affinity for water.

The following procedure readily demonstrates the effectiveness of Graham's Salt (Calgon) as a dispersant. Select two beakers of 500 or 600 cc. capacity and to each of them add 100 cc. of distilled water. To one beaker add 0.75 Gm. of Calgon and stir until dissolved. To each beaker add 100 Gms. of titanium dioxide (Titanox-A) and stir until all the particles have been wetted, noting that the pigment in the first beaker bearing the Calgon will be more easily wetted than is the contents of the second beaker. Invert the second beaker and observe that the slurry is too thick to pour whereas the Calgon bearing slurry is thin and mobile. This experiment may be repeated with any of the aforementioned metallic oxides and pigments. The fruitful use of sodium polyphosphate in a pharmaceutical sense is the ability of increasing the solid content of a sun screen agent without increase of viscosity.

Dilatancy is a property of a system of closely packed particles in a liquid medium characterized by an increased resistance to deformation upon sudden application of an external force. The following definition is quoted from Webster and may be helpful in understanding these properties more fully. "Di-lat'-ant (a as in lay) Expanding, having the property of increasing in volume when changed in shape, owing to increase of the space between the particles." Under these conditions the packing can only become looser and consequently liquid is sucked in which leaves the mass of solid apparently dry and hard. When the pressure is released, the whole mass becomes moist and fluid again. Wet sea sand when stepped upon suddenly, becomes

firm, appears dry upon the surface and resists indentation; when the foot is removed, it again appears moist and loses its rigidity. Particles in most naturally dilatant systems are more or less spherical and hence interfere less with each other than would unsymmetrical (anisometric) particles.

Thixotropy is explained as the formation of a mechanical structure or house of cards by the orientation of the particles, which structure is readily altered by an external force, that is, the viscosity changes with increased velocity of motion. One might imagine a system in which the particles are represented as platelets or a deck of cards which when added to a liquid, present a slurry with their faces lying super-imposed upon one another. When gently stirred they readily pass over each other's surfaces with the minimum amount of energy imparted, but when they are violently stirred they rearrange themselves in a helter-skelter manner offering considerable resistance to the external force applied. That is the viscosity changes with increased velocity of motion.

Rheopexy is a form of thixotropy in which certain sols solidify as a result of a regular gentle motion instead of vigorous shaking.

Quite a number of systems exhibiting these phenomena have been described in the literature of the past. The mud employed in the rotary drilling of oil wells is composed of swelling-type clays. This mud pumped down inside the drill stem picks up the cuttings from the drill bit and returns to the surface around the drill stem. When the mud flow stops for any reason, the mud gels and holds the cuttings which otherwise would settle and bind the drill stem. When the mud flow is resumed, this gel fluidizes. Thus thixotropy has an important industrial application.

A kaolin with anisometric particles mostly below one micron produces a suspension, when mixed with 1.6 ml. 2 *N* NaCl per gram kaolin, which has a spontaneous (thixotropic) solidification of 17 minutes. Upon tapping the solidification or rheoplectic value is reduced to 30 seconds and by irradiation in an ultrasonic field may be reduced to 15 seconds. Gypsum water paste solidifies normally in 10 minutes, but sets in a few seconds when gently tapped (rheopexy). Vanadium pentoxide behaves similarly.

Dilatancy may be demonstrated by selecting an 800 to 1000 cc. beaker to which may be added 40 cc. of distilled water, 10 cc. of a 5% zinc nitrate solution and 20 cc. of a 5% Calgon solution. To this

solution there is slowly added 200 grams of precipitated calcium carbonate while the stirring is continued by the aid of a stainless steel spatula stopping the addition when the suspension becomes dilatant. This property is recognized by the following behavior. When the slurry is slowly stirred it is very fluid but when stirred rapidly there is a strong resistance to the imparted energy. When the spatula is inserted slowly there is little resistance offered but when the stirrer is hastily withdrawn it is accompanied by a sucking noise. If the slurry is then poured from a height of two feet into a second vessel one notes a wavy jagged stream indicative of stiffening. Finally if the mass be rolled into the form of a ball during which time a stiffening action can be felt, then the mass forcibly hurled against a solid object it will be shattered as is a solid. The fragments left to remain *in situ* will then collapse into a liquid state. The exact amount of calcium carbonate required for formulation of the slurry is dependent upon the physical characteristics of the product used. Dilatant slurries range from 67% by weight (142 Gm. of precipitated calcium carbonate) to 80% by weight (260 Gm. of CaCO_3). The zinc nitrate may be replaced with sodium aluminate, potassium titanium oxalate, lead acetate and barium chloride.

CITRIC AND GLUCONIC ACIDS

Citric and Gluconic acids (Chas. Pfizer & Co., Inc.) have been made available to meet the need of sequestrants for the pharmaceutical and food industries. Citric acid is available in the anhydrous and the hydrated forms. Sodium citrate has a similar existence. Gluconic acid is available as a technical grade 50% aqueous solution. It is light brown in color, slightly viscous and possesses a slight acetous odor. Glucono-delta lactone is one of the inner anhydrides formed by the removal of one molecule of water from a molecule of gluconic acid. It occurs as a free flowing, white crystalline powder. Upon the addition of water gluconic acid is formed. Two grades of sodium gluconate are available—the technical and the highly refined salt. Ammonium gluconate is available as a neutral salt but it is subject to decomposition upon steaming. Elsewhere in this paper the sequestering power of a number of compounds has been stated. Gluconate is relatively ineffective as a sequestrant for calcium in pH ranges below 11. The citrate compares favorably with sodium polyphosphate and

an ethylene tetra-acetic acid derivative. In the presence of free caustic soda, the gluconate is the preferred sequestrant. Tests have shown that sodium gluconate will sequester iron in a caustic soda solution of 35% strength. The iron gluconate complex is stable at boiling temperatures. The citrate is also satisfactory as a sequestrant for iron though not quite as satisfactory as the gluconate. The citrate is more satisfactory below a pH of 7. Sodium citrate is most effective as a complexing agent for nickel in a pH range of 7 to 11. Both citrates and gluconates effectively sequester copper at various pH's; however, the citrate is the more effective for pH ranges above 7. For barium, sodium citrate is more effective than the gluconate in the normal pH range and in the presence of 1% of sodium hydroxide solution. Sodium Gluconate complexes 10 parts of lead per 100 parts of agent at a pH of 7. Its efficiency is increased as the pH is elevated or lowered. Sodium citrate will sequester approximately 5 parts of lead per hundred parts of agent over the entire range.

OTHER COMPLEXING AGENTS

Nitrilo Triacetic acid or triglycin $N(CH_2COOH)_3$ (700) has enjoyed some commercial success but its complexes are less stable. There is no reason why chelation in the oxygen series could not be extended as far as in the amino series except for the difficulty of synthesis. Ethylene bis-tartronic acid is a chelate of this nature. The functional groups may be attached to a benzene ring as in gallic acid 3,4,5 trihydroxy benzoic acid (40) * and in Nitro-resorcinol $1-NO_2C_6H_3-2,4-(OH)_2$ (320). In mandelic acid $C_6H_5CHOHCOOH$ (10) the benzene ring has been substituted in the aliphatic compound without materially altering its sequestering value. The functional groups may also form part of a heterocyclic ring as in dehydromucic acid furan-2,5-dicarboxylic acid and furoic acid $HC=CHCH=C(COOH)O$ (14), where the furane ring is used.

[]
(These are weaker) than glycolic $HOCH_2COOH$ (6) and diglycollic acid $(HOOCCH_2)_2O$ (170). The dicarboxyimidazole $HOOC-C(COOH)N=CHNH$ (170) forms an analogue to

[]
methylamino diacetic acid $(CH_3N(CH_2COOH)_2$ (180) while

* The letters in parentheses represent the sequestering power (millimoles of calcium chloride per mole of sequestrant).

alloxan (75) appears to be unique NHCONHCOCOCO . The

resonating structure of quinone quinone tetrathiolglycollic acid $\text{C}_6\text{O}_2(\text{SCH}_2\text{COOH})_4$ (100) has a greater sequestering potency than the weak thioglycollic acid (0.5) or quinone tetracarboxylic acid $\text{C}_6\text{O}_2(\text{COOH})_4$. In comparing the relative potency of the primary groups, the nitroso appears to be the most potent, and is followed by the nitro and the carboxy nitrosoresorcinol (320) 1- NOC_6H_3 -2,4(OH) $_2$, Picric acid 2,4,6-(NO $_2$) $_3\text{C}_6\text{H}_2\text{OH}$ (80) and quinone tetracarboxylic acid (140) $\text{C}_6\text{O}_2(\text{COOH})_4$. The coordinating groups may be arranged in the following order of potency: $=\text{O}$ is less than $\text{OH}=\text{NH}_2$ is less than $-\text{C}=\text{C}-$ is less than SH , and is illustrated in pyruvic CH_3COCOOH and lactic acid $\text{HOCHCH}_3\text{COOH}$ (6); glycine $\text{H}_2\text{NCH}_2\text{COOH}$ (4) glycollic acid HOCH_2COOH (6) and thioglycollic acid HSCH_2COOH (0.5) and aspartic acid $\text{HOOCCH}_2\text{CH}(\text{NH}_2)\text{COOH}$ (35) malic Acid $\text{HOOCCHOHCH}_2\text{COOH}$ (35) and maleic acid $\text{HOOCCH}=\text{CHCOOH}$ (20). The diazo group of diazomalonic acid (140) is particularly powerful. Pyromellitic acid C_6H_2 -1,2,4,5-(COOH) $_4$, ethylenediamine tetraglycol (HOCH_2CH_2) $_2\text{N}-\text{CH}_2\text{CH}_2\text{N}-(\text{CH}_2\text{CH}_2\text{OH})_2$ and diacetyl $\text{CH}_3\text{COCOCH}_3$ lack sequestering power.

Summary

Much literature has appeared during the last decade pertaining to sequestering agents. Many new applications will arise as time advances. Ethylenediamine tetra-acetic acid is a high melting point solid (240°C), insoluble in hot or cold water as well as in the ordinary organic solvents. It is soluble in formamide and it dissolves in the stronger mineral acids of 10% strength or greater. It forms a series of water soluble salts of sodium, but these as potassium, ammonium and alkylamine salts are insoluble in ethanol containing less than 10% water. Unlike the polyphosphates, they do not precipitate quaternary ammonium compounds or proteins. They are mildly surface active, but possess no thinning action on starches or clays. The sodium salts do not hydrolyze in water, acid or alkali, but are decomposed by electrolysis and are also attacked by strong oxidants such as the hypochlorites, etc. They are stable to mild oxidants and possess anti-oxidant properties by removal of catalyzing agents from solution.

Ethylenediamine tetra-acetic acid undergoes many of the reactions typical of organic acids: it condenses with amines to form amides and with alcohols to form esters. If Versene or Sequestrene (Alrose Chem. Co., Providence 1, Rhode Island) the tetra sodium salt is added to a soap, no cloudiness appears upon dilution with water containing calcium ion. The same sodium salt will also dissolve the very slightly or sparingly soluble Calcium Oxalate. The precipitation of ferric hydroxide in dilute sodium carbonate or ammonia is prevented, but such is not the case in the presence of 1% sodium hydroxide.

Dyckerhoff reported that 0.06-0.1% ethylenediamine tetra-acetic acid prevented the coagulation of human blood *in vitro* but not *in vivo*. Martin demonstrated that it had a more prolonged effect than citric acid on the keeping qualities of blood.

Concentrations of calcium gluconate in water can be effected up to 20%, the normal solubility being but 3%.

Currently in the experimental stage is the use of the disodium versene for dissolving kidney stones. Although citric acid is effective for dissolving calcium phosphate calculi, Sequestrene dissolves stones of calcium oxalate as well.

The addition of Sequestrene to quaternary ammonium germicides for general hospital and surgical use is indicated for application in hard water areas.

Sequestrene or Versene may also be of value as a detoxicant in cases of heavy metal poisoning.

The agent may also be used for the intraconversion of protein heavy metal complexes to that of the sodium salt.

Chemical incompatibilities in pharmaceutical formations are sometimes due to the formation of insoluble precipitates herewith illustrated:

Acacia and other gums with iron, lead, calcium, magnesium and other heavy metallic salts.

Tannic acid with iron and other heavy metals.

Apormorphine Hydrochloride with iron salts.

Barium chloride with sulfate or phosphate.

Iron salts with vegetable astringents, carbonates, bicarbonates and alkaloidal salts.

Other incompatibilities due to discoloration as the reaction of iron with acetanilide, creosote, benzoate, antipyrine, resorcinol, salicylic acid and oil of wintergreen.

The oxidation of many organic materials, such as mercaptans, aromatic amines, etc., as in the case of ascorbic acid, is catalyzed by trace metals.

Toxicity: Information on the physiological properties of the Versenes and Sequestrenes shows that they appear to be relatively non-toxic when administered orally or applied to the skin. The toxicity of the material administered intravenously or intramuscularly require further study.

Added to stearate soap Sequestrene or Versene exhibits some very interesting effects which apparently are not related to its water softening propensities. First small amounts alter the gel structure in cold distilled water, the viscosity drops and the transparency increases.

Traces of cobalt, iron, copper, chromium, and manganese affect the keeping qualities of soap; cobalt traces will turn a soap rancid in 20 hours.

Sequestrene is suggested as a clarifier in aqueous solutions of the alkalis. Bottles of ammonia may be kept clear by the addition of a small amount of sequestrant.

It is suggested for use with the liquid soap shampoos for reasons heretofore described. It is suggested for use in cuticle removers and the wave solutions containing thioglycollates. There is some evidence that it has a solvent action on tartar deposits of the teeth.

For the complete softening of water, 1 gram of reagent of Sequestrene-4 is required to treat one gallon of water of four grains hardness. Actually, complete water softening for laundry purposes is not required and less Sequestrene-4 may be used.

Ethylenediamine tetra-acetate disodium salt is used as an analytical reagent for the titration of calcium ions. This method was developed by Schwarzenbach. Eriochromeschwartz-T is the indicator used.

Hexametaphosphate is fatal when injected intravenously at the rate of 130 mg. per kilo body weight; death is presumably due to heart block presumably by deionizing the blood calcium. Rats fed 2 Gm. of Graham's Salt daily were healthy and gained in weight but when fed double this amount diarrhea developed and the intestines hemorrhaged.

OTHER APPLICATIONS

Schwarzenbach has emphasized the usefulness of chelating agents as metal buffering agents in maintaining a nearly constant concentration of metal ion at almost any level of concentration. In order to accomplish this, a metal chelate is formed in the presence of excess chelating agent.

The estimation of metal ions by simple titration methods in solution involves the problem of selecting a reagent which combined with the metal strongly enough to give a sharp end point. The estimation of hydroxyl ions or hydrogen ions, and hence strong acids or bases in solution, may be carried out by titration of one by the other because of the high affinity of H for OH. In a similar manner hydrogen ions may be estimated by titration with cyanide ion or any strong base. On the other hand the titration of a metal ion with a strong base such as cyanide ion does not result in a sharp end point. This seems to be due to the fact that a single cyanide ion is not bound to the metal as strongly as is hydrogen and also to the fact that the metal-cyanide reaction is a stepwise series of four (more or less) reactions with no sharp breaks in between them.

USE OF pH INDICATORS IN METAL TITRATION

After selection of a chelating agent which will give a sharp inflection in the curve of pM (i.e., negative log of M) vs. moles of chelating agent added, it is necessary to select an indicator which is sensitive to the concentration of the metal ion. Since chelating agents are themselves bases, an acid base indicator is satisfactory in many cases. The sudden decrease of the concentration of metal at the end point, resulting from the addition of chelating agent anion to a solution of the metal ion, is accompanied by a sharp rise of pH. Thus a typical pH indicator selected to correspond to the pH range of the steep portion of the pM curve would be satisfactory. The same result may be obtained by adding an alkali hydroxide to an acid or neutral solution containing the metal ion and an excess of the acid form of the chelating agent. Both of these procedures were applied to the estimation of metals with ammonia triacetic acid by Schwarzenbach and Biederman. They titrated various metals with alkali hydroxide in the presence of excess of the dipotassium salt of ammonia triacetic acid. Titrations of the metal salts were also carried out by the use of the highly alkaline tripotassium salt of am-

monium triacetic acid. During the addition the solution remained acidic.

Similar methods have been outlined for the titration of metals with Uramil diacetic acid or (amino-barbituric acid-*N,N*-diacetic acid) which was found to behave in a manner similar to ammonia triacetic acid with the exception that Mg. was more easily titrated because of its more highly chelate stability constant. Schwarzenbach also described the use of various dyes, which he calls metal indicators, for the titration of various metal ions. These indicators show a marked color change when the concentration of the metal ion is changed, and are soluble in the titration medium. Ammonium purpurate also called murexide, is the oxidation product of dibarbituryl amine. The effect of calcium ion concentration on the light absorption of purpurate at pH 11.2 indicates a color changing from red-violet through violet to blue of the free dye whereas for the metal chelate there is a color change from the yellow orange through red-orange to red. Murexide is therefore a strong enough chelating agent to act as pM indicator for Ca, Mg, Cd, Zn and Cu. It has also been suggested for the determination of scandium.

A number of *o-o'*-dihydroxyazo dyes and particularly one known as Eriochromeschwarz-T (Schultz-Lehman 241) have been investigated as metal indicators. The structure of the dye indicates the presence of two ionizable hydrogens, and the compound exists in three differently colored species in solution. It is therefore a pH indicator with two sensitive regions of color change from wine red through blue to orange. Chelation with a metal ion results in the displacement of two protons with one or more additional covalences satisfied with other donors such as water molecules. The second reaction takes place to practical completion in the pH range 8 to 10 and gives a color change from blue to red which lends itself well to visual determination.

Titration procedures using this indicator for Mg, Ca, Sr, Zn and Cd with Eriochromeschwarz-T wherein the metal solution after buffering with $\text{NH}_3\text{-NH}_4\text{Cl}$ to a pH of 10 was titrated with the disodium dihydrogen ethylenediamine tetra acetate standard solution. The dye color originally wine red in the presence of metal ion, suddenly changes to blue at the end point, since the chelation with EDTA is stronger for these metals than with the indicator. Since Pb, Mn and Hg precipitate at pH of 10.0 these metals are first treated with excess EDTA, buffered at pH of 10.0 and then the solution back titrated with

standard Mg^{++} solution. In this way a color change from blue to red is obtained. Co, Cu, Ni, Fe, La, and Ce could not be titrated directly since the dye chelate was either too stable or did not dissociate rapidly enough. This titration method has developed into a rapid and very accurate method for the determination of total hardness of water. Briefly the analysis depends upon the formation of a wine-red Mg chelate of the dye, which is less stable than the Mg chelate of ethylenediamine tetra acetic acid. Since the equilibrium is shifted far to the right at pH of 10.0 the addition of reagent causes a sharp color change from red to blue. When hard water containing both Ca and Mg ions is titrated with EDTA as the tetra sodium salt the solution is initially wine red since the dye combined preferentially with Mg. As the standard chelating agent is added, free Ca ions are removed first, since the stability constant of the calcium chelate is greater than that for Mg. At the end point all of the free Ca and Mg have been removed in the form of their water soluble chelates, and further addition of the standard reagent results in removing Mg from the dye, producing the indicator color change. Thus the total water hardness (Ca and Mg) is determined.

CHELATION AND SEQUESTRATION IN THE BIOLOGICAL SYSTEMS

It has been known for some time that many important catalysts are metallic compounds of which the simplest and most rudimentary are simple inorganic salts of metals capable of existing in more than one oxidation state. Ferrous salts are known to catalyze the decomposition of hydrogen peroxide and organic peroxides. The ability is due to the capability of transferring electrons. The functions of heme proteins such as electron transfer and decomposition of peroxides are present in elementary form in the simple hydrated ions. The special chelate structure of the heme protein, imparts to the metal many properties of great biological importance not present in the simple ionic form. Catalytic activity is present in other metals; simple copper salts are known to catalyze the oxidation of ascorbic acid. Many enzymes are dependent on the presence of various metals such as Cu, Mn and Co for carrying on their specific catalytic functions. Mg does not probably exist in more than one state of valence yet it may react with a particular chelating agent, such as a protein and in so doing cause chemical changes in the chelating agent. The catalytic metal chelates fall into three classes: 1. Those which are oxidation-reduction catalysts which may or may not undergo a

valence change. These are not permanently altered. 2. In some cases the chelating agent involves a chemical change as in the catalytic oxidation of the oxalates or the more rapid reaction of the chelating agent with another reagent as the result of chelation as in the bromination of ethyl acetoacetate and the building up or breaking down of the chelating agent to give a chelate of more favorable structure. Under this classification would come certain hydrolytic enzymes and enhanced formation of chelating agents in the presence of strongly chelated metal ions. 3. In addition to the aforementioned there is the negative catalysis of chelating agents whereby the rate of the chemical reaction is reduced, probably through combination of the metal ions which are the true catalysts for a particular reaction.

In general the uses of unnatural chelating agents in biological systems may be divided into three groupings:

1. The destruction of organism by chelation of essential metals—bactericidal and fungicidal action.
2. Inhibition of certain metals and metal enzymes for the purposes of studying functions of metals and enzymes in biological media.
3. Removal of harmful metals from living organisms.

Other widespread uses of Chelating Agents are as algacides, antioxidants, boiler scale removal, clarification of liquids such as soaps and wines, cleaning of metal objects by the removal of rust, scale and food deposits, detergent additive, dyeing of fabrics, electrodeposition of metals, emulsion polymerization, flotation agents, germicides, medicinals, prevention of rancidity, and side reactions in the purification of chemicals, lubricating oils, removal of spray residue, stabilization of peroxides, vitamin-C, water softening, decontaminant of radioactive isotopes and metals, analysis by separation, precipitation and colorimetry, control of metal ion concentrations, deactivation of enzymes, determination of configuration of optically active compounds, elimination of metal ions from animals, oxygen carriers in a biological system as with co-histidine, bis-salicylethylenediamine and Co^{++} , the quantitative determination of amino acids by filter paper chromatography, the separation of metals by solvent extraction, by elution of cation, exchangers, fractional precipitation (in presence of aqueous chelate), the study of the nature of metal ions in solution and the titration of metals, the thinning of slurries, etc. Other applications will arise when more investigators study the virtues of the chelating agents.

SELECTED ABSTRACTS

Successful Use of Chloramphenicol in the Treatment of Typhoid. Balim, A. I., and Gronbeck, C., Jr. *U. S. A. F. Med. J.* 5:68 (1954). Chloramphenicol (Chloromycetin) was used in the treatment of the victims of a typhoid epidemic among Turkish soldiers. All of the soldiers had been inoculated against typhoid, typhus, and smallpox upon entering the service. A group of 48 patients with typhoid were given 2 Gms. of chloramphenicol the first day and 1 Gm. daily thereafter until two days after the temperature was normal.

This treatment was completely successful initially, but 10 of the 48 patients had one or more relapses. However, all of the patients having relapses responded as well to the antibiotic at the time of the relapse as they had initially. Ten of the patients each received an average of 5 Gms., 22 an average of 7 Gms., and 6 an average of 12 Gms. The ten patients that relapsed each received an average of 12 Gms., but their initial response had been achieved with an average of 6 Gms.

The authors stated that there was no evidence of drug resistance or of toxicity. They also concluded that the fact that there were no deaths among these patients indicated that the dosage level, although rather low, was adequate. Prior to the advent of chloramphenicol the mortality rate of patients with typhoid under similar circumstances was about 10 per cent.

The Effect of Polyvinylpyrrolidone as a Retardant of Drug Action. Graham, D., Slinger, R., and Teed, H. *J. Pharm. Pharmacol.* 6:115 (1954). Interest has existed in the retarding effect of polyvinylpyrrolidone (PVP) on the absorption and effect of various drugs. The authors studied the effect of various concentrations of PVP on the absorption and effect of three of the more common analgesics given by injection.

The test animals employed were rats. The injections were given either intramuscularly or subcutaneously. The dose of morphine sulfate employed was 4.0 mg. per Kg., that of meperidine hydrochloride was 32 mg. per Kg., and that of methadone hydrochloride was 2.5 mg. per Kg. These drugs were dissolved in various concentrations of PVP in distilled water. The concentrations used were 0.0, 5.0, 10.0, 20.0, and 40.0 per cent.

Under the conditions of these tests there was no marked influence on the duration of action or potency of the drugs, either by intramuscular or subcutaneous administration. In some tests using the 40 per cent concentration of PVP there appeared to be a delay in the onset of analgesia, particularly after intra-muscular injection. The 40 per cent solution of PVP is very viscous and quite difficult to handle. This latter factor would probably rule out the use of such high concentrations of PVP. It would thus appear that PVP is of little or no value as a retardant for the analgesics used in these tests.

Suppression of Postpartum Lactation With TACE. Hendricks, C. H. *J. Clin. Endocrinol. Metab.* 14:339 (1954). The new synthetic chemical TACE (chlorotrianisene), having actions like the female sex hormones, was used in the suppression of postpartum lactation in 60 patients. Breast pain was relieved in 93 per cent of the women treated with this compound and followed for a period of at least eight weeks. The drug was administered beginning on the first postpartum day and continued for seven days. A dose of 12 mg. was given four times a day.

The drug is apparently stored in the body fat and then released gradually over a more prolonged period of time. The estrogens are not so stored and thus the effect from the latter is more brief. The author also pointed out that no withdrawal bleeding occurred following the discontinuation of therapy. This is a symptom frequently encountered after estrogen therapy. Thus it would appear from this relatively small number of cases that TACE has value in the suppression of postpartum lactation and has certain advantages over the estrogens in such treatment.

ISUPREL

This drug
will suppress almost
any attack of

ASTHMA

Herzfelder, Herbert:
Lancet, 1/13/37, June 23, 1951.

5,500,000 people
in the United States
suffer from
bronchial asthma
sometime in their
lives.*



More doctors are prescribing ISUPREL—most potent bronchodilator—for all types of asthma every day because ISUPREL acts almost instantaneously.

ISUPREL solution is administered by means of De Vilbiss nebulizer No. 40 or 41.

ISUPREL is heavily advertised . . . *ethically* . . . in leading medical journals, by mail . . . by detailing.

ARE YOUR STOCKS ADEQUATE?

*Dubin, L. I.: Statistics of bronchial asthma. In: Derbes, V. J., and Engelhardt, H. T.: The Treatment of Bronchial Asthma. Philadelphia, Lippincott, 1946, Chapter 3.

ISUPREL®
HYDROCHLORIDE

Winthrop Stearns INC.
1450 Broadway, New York 18, N. Y.
PHARMACEUTICALS IN DAILY DEMAND
ETHICALLY ADVERTISED AND DETAILED

WITH PHYSICIANS IN RESEARCH AGAINST
ALLIED DISEASE ★
PHARMACEUTICALS



American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

Former Editors of the Journal have been: Daniel B. Smith, 1825-1828; Benjamin Ellis, 1829-1831; Robert E. Griffith, 1831-1836; Joseph Carson, 1836-1850; William Procter, Jr., 1850-1871; John M. Maisch, 1871-1893; Henry Trimble, 1893-1898; Henry Kraemer, 1898-1917; George M. Beringer, 1917-1921, and Ivor Griffith, 1921-1941.

Established and maintained as a record of the progress of pharmacy and the allied sciences, the Journal's contents and policies are governed by an Editor and a Committee on Publications elected by the members of the College.

Manuscripts should be sent to the Editor, who does not assume any responsibility in connection with the views or investigations of contributors of accepted manuscripts, other than to exercise general care in selection.

Contributors are allowed a reasonable number of copies of this Journal, free of charge, if applied for when the proof is returned.

Reprints, if desired, should be ordered when the proof is returned. The table below shows the *approximate* cost of reprints, the make-up of the pages to be identically the same as in the Journal. The actual cost may vary from the figures given, and will depend upon the amount of presswork, paper, binding, and other factors. Reprints containing half-tones may be expected to cost somewhat more than the rates given.

	2 pp.	4 pp.	8 pp.	16 pp.	COVERS WITH TITLES	
50 copies.....	\$ 4.50	\$10.00	\$16.25	\$27.50	50 copies.....	\$ 7.50
100 "	7.50	13.75	21.25	40.00	100 "	12.50
250 "	10.00	17.50	27.50	53.75	250 "	17.50
500 "	15.00	25.00	35.00	68.75	500 "	26.25

cancer

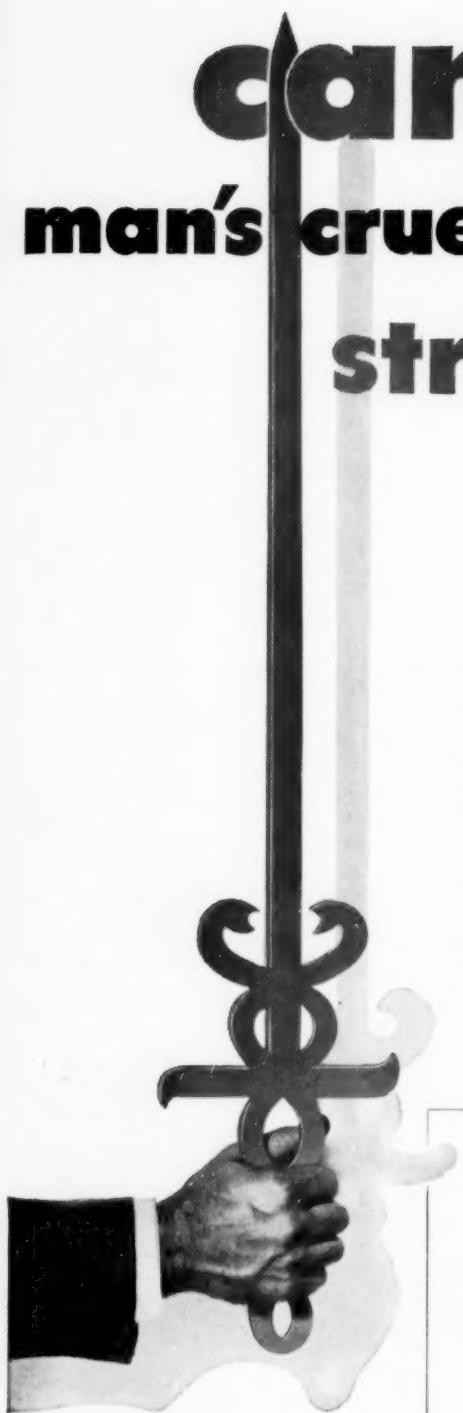
man's cruelest enemy

strike back

THE FIGHT against cancer is being waged ceaselessly in the research laboratory, in the hospital, the doctor's office. With new methods of diagnosis and treatment, medical science now has weapons to combat man's cruelest enemy more effectively than ever.

THESE LIFESAVING ADVANCES have been made possible by the generous contributions of your fellow Americans. To them the Sword of Hope, symbol of the American Cancer Society's attack through research, education and service to patients, gives assurance of continuing progress today . . . of greater gains tomorrow.

JOIN WITH THEM in striking back with a gift to the American Cancer Society.



American Cancer Society

GENTLEMEN:

- ☐ Please send me free information on cancer.
☐ Enclosed is my contribution of \$.....
to the cancer crusade.

Name.....

Address.....

City..... State.....

Simply address the envelope:

CANCER c/o Postmaster, Name of Your Town